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Preparation, physicochemical characterization, dissolution and formulati studies of irbesartan cyclodextrin inclusion complexes: Comparison between ß-CD & HP-ß-CD

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ABSTRACT

Evaluation of inclusion complexes of irbesartan with ß-cyclodextrin and hydroxypropyl-ß-cyclodextrin, for dissolution properties and its tablet formulation were studied. Phase solubility curve was A_L type for evaluation of stoichiometry. The prepared complexes were characterized by Fourier-transform infrared spectroscopy, differential scanning calorimetry and powder x-ray diffraction studies. The result of present findings clearly indicates maximum improvement in dissolution of irbesartan with the complex prepared with hydroxypropyl-ß-cyclodextrin with the kneading method. Various dissolution parameters point out the significant difference between the release profile of pure irbesartan and its complexes especially with hydroxypropyl-ß-cyclodextrin. The more hydrophilic nature of hydroxypropyl-ß-cyclodextrin might be responsible for better complexation and greater solubility of irbesartan. Even formulation studies too, the hydroxypropyl-ß-cyclodextrin-irbesartan complex showed a better dissolution profile over ß-cyclodextrin.

Keywords: Irbesartan, ß-cyclodextrin, hydroxypropyl-ß-cyclodextrin, inclusion complexes, dissolution studies.

INTRODUCTION

Irbesartan (IRB) (2-butyl-3-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one; see Fig. 1) is an orally active specific angiotensin II, AT_1 receptor antagonist, and clinically effective drug in the treatment of hypertension.[1] It is slightly soluble in alcohol and methylene chloride and practically insoluble in water. Due to its hydrophobic nature (octanol/water partition coefficient 10.1 at pH of 7.4) IRB shows low dissolution profile in gastrointestinal fluid resulting poor absorption, distribution & consequently poor target organ delivery.[2] Improvement of aqueous solubility in such cases shall lead to improved therapeutic efficacy of the drug.

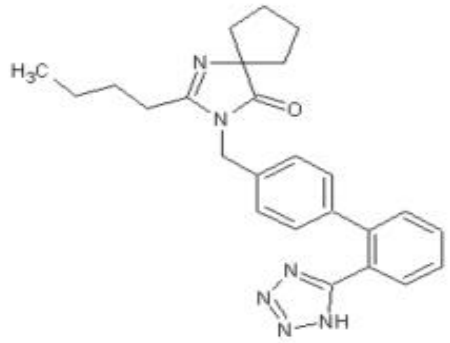

Fig 1: Structural formula of Irbesartan

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Cyclodextrins (CD's) with their cylinder-shaped cavities capable to form inclusion complexes with a wide range of commonly used drugs by taking the whole molecule or part of it into the cavity and known to improve the aqueous solubility of drugs. Many drugs such as hydrocortisone, itraconazole, omeprazole, mitomycin, nitroglycerin, voriconazole etc. have been complexed with CD's and formulated for enhancing solubility and therapeutic activity. [3-4] Even IRB ß-cyclodextrin (ß-CD) complex has been reported to enhance its solubility. [5]

ß-cyclodextrin and its more hydrophilic derivative hydroxypropyl-ß-cyclodextrin (HP-ß-CD) have been selected for the complexation study of Irbesartan and also for their comparison. The latter was successfully used for the solubilization of the closely related drug valsartan.[6] In the present study inclusion complexes of IRB with ß-CD and HP-ß-CD were prepared by kneading, co-evaporation and physical mixing and characterized by Fourier-transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) with the aim of improving the aqueous solubility and dissolution profile of the IRB. Further to demonstrate experimentally HP-ß-CD, a more hydrophilic derivative can be more useful to achieve greater solubility.

MATERIALS AND METHODS:

Materials

HP-ß-CD (Mole. Wt. 1500) and ß-CD (Mole. Wt. 1135) were generous gift from Gangwal Chemicals Pvt. Ltd. Mumbai. India. Irbesartan was received as a gift sample from Panacea Biotec, (Chandigarh, India). Lactose monohydrate, microcrystalline cellulose, croscarmelose, silicone dioxide, magnesium stearate and sodium lauryl sulphate were purchased. All chemicals and solvents used in this

study were of A.R. grade. Freshly prepared double distilled water was used throughout the work.

Phase solubility study

Phase-solubility studies were performed by the method of Higuchi and Connors.[7] IRB, in constant amounts (5 mg) that exceeded its solubility, was transferred to screw capped vials containing 15 ml of aqueous solution of ß-CD or HPß-CD at various molar concentrations (0, 3.0, 6.0, 9.0, 12.0, and 15.0 mM). The contents were stirred on rotary shaker (Remi, India) for 72 hrs. at 37 ^{0}C ± 0.1 ^{0}C and 300 rpm. The time duration was fixed based on pilot experiment and found to be sufficient to achieve equilibrium of mixture.

After reaching equilibrium, samples were filtered through a 0.22 µm membrane filter, suitably diluted and analyzed spectrophotometrically for drug content at 230 nm (Jasco-V 530, UV/Visible spectrophotometer, Jasco Inc., Japan). Solubility studies were performed in triplicate.

Preparation of inclusion complexes

Irbesartan and CD's were sieved through 120 # prior to their use. Complexes of ß-CD and HP-ß-CD with IRB were prepared in the molar ratio of 1:1 by different methods mentioned below. For better identification, the samples are designated with different abbreviations (Table 1).

Physical mixture: Physical mixture (PM) of CD's and IRB were prepared by simply mixing powders with a spatula for 15 min and then sieved through 120 #.

Co-evaporation method: For preparation of complexes by co evaporation method CD's and IRB were mixed in 1:1 molar ratio, 5 ml of methanolic solution of IRB was added slowly to 5 ml of the aqueous solution of CD followed by stirring at 300 rpm using magnetic stirrer at 37^{0}c for 24 hrs. The solvents were then evaporated at 45-50 ^{0}C. The resultant solids were pulverized and then sieved through 120 #.

Kneading method: For preparation of complexes by kneading method, the CD and IRB were taken in 1:1 molar ratio. The CD was triturated in a mortar with small quantity of water to obtain a homogeneous paste. IRB was then added slowly while grinding; a small quantity of methanol was added to facilitate the dissolution of IRB. The mixtures were then grounded for 6 hrs. During this process, an appropriate quantity of water was added to the mixture to maintain a desired consistency. The pastes were dried in an oven at 45-50 ^{0}C for 24 hrs. The dried complexes were pulverized and then sieved through 120 #.

Determination of Drug content in complexes

The samples of complexes and physical mixtures were assayed for IRB content by dissolving a fixed amount of the complexes in methanol and analyzing for the IRB content spectrophotometrically at 230 nm.

Characterization of complexes

Fourier transform infrared (FTIR) spectroscopic analysis: FTIR spectra of moisture free powdered samples of IRB, CD's, its PM's and complexes with ß-CD and HP-ß–CD were taken using a FTIR spectrometer (Shimadzu FTIR 8400) by potassium bromide pellet method.

Powder X-ray diffraction (PXRD) analysis: Powder X-ray diffraction patterns of all samples were determined using Powder X-ray diffractometer (Phillips 1879 Netherlands), at a scan rate of 1^0 min^{-1} from 2θ range from 5^0 to 50^0.

Differential scanning calorimetry (DSC) analysis: DSC scans of all powdered samples were recorded using Mettler Toledo DSC-823 DSC module controlled by STAR SW 9.01 software (Mettler, Switzerland). The samples (3 –7 mg) were accurately weighed in crimped aluminum pans, before heating under nitrogen flow (40 ml/min) at a scanning rate of 10 ^{0}C /min, over the temperature range of 30 ^{0}C to 300 ^{0}C. An empty aluminum pan was used as a reference.

Dissolution Studies

Dissolution studies of IRB in powder form, its PM's and complexes with ß-CD and HP-ß-CD were performed to evaluate drug release profile. Dissolution studies were performed on USP dissolution apparatus type II with 900 ml dissolution medium 0.1 N HCl (pH 1.2) at 37 ^{0}C ± 0.5 ^{0}C at 100 rpm for 4 hr. At fixed time intervals 5 ml aliquots were withdrawn, filtered, suitably diluted and assayed for IRB content by measuring the absorbance at 230 nm. (Pilot experimental data indicated no change in the λ_{max} of IRB due to the presence of CD's in the dissolution medium.) Equal volumes of fresh medium (pre-warmed to 37 ^{0}C) were replaced into the dissolution medium to maintain constant volume throughout the test period. Dissolution studies were performed in 6 replicates, and calculated mean values of cumulative drug release were used while plotting the release curves.

Formulation studies

Tablets containing 150 mg of IRB were prepared by direct compression using different excipients like Lactose monohydrate, colloidal silicon dioxide, and magnesium stearate. Tablets containing complexes (equivalent to 150 mg IRB) prepared by kneading and co-evaporation method were also prepared similarly using less quantity of lactose. The blend was compressed on a six-station single rotary machine (Jaguar, India) using round-shaped, flat punches to obtain tablets having thickness 3–4 mm and hardness 3–5 kg/cm^2. The tablets were studied in 6 replicates for release profile of IRB using the same method described in dissolution studies.

Statistical analysis

Model independent mathematical approach proposed by Moore and Flanner [8] for calculating a similarity factor f_2 was used for comparison between dissolution profiles of different samples. The similarity factor *(f_2)* is a measure of similarity in the percentage dissolution between 2 dissolution curves and is defined by following equation:

$$f_2 = 50 \times \log\left\{[1+(1/n)\sum_{t=1}^{n}(R_t-T_t)^2]^{-0.5}\times 100\right\}$$

where n is the number of withdrawal points, Rt is the percentage dissolved of reference at the time point, t and Tt is the percentage dissolved of test at the time point t. A value of 100% for the similarity factor *(f_2)* suggests that the test and reference profiles are identical. Values between 50 and 100 indicate that the dissolution profiles are similar whilst smaller values imply an increase in dissimilarity between release profiles. In order to understand extent of improvement in dissolution rate of IRB from its complexes and physical mixture, the obtained dissolution data of pure IRB, it's PM and complexes with CD's were fitted into equation.

$$MDT_{in\text{-}vitro} = \frac{\sum_{i=1}^{n} t_{mid}\,\Delta M}{\sum_{i=1}^{n}\Delta M}$$

Here, i is dissolution sample number, n is number of dissolution times, t_{mid} is time at the midpoint between times t_i and t_{i-1}, and $\triangle M$ is the amount of IRB dissolved (µg) between times t_i and t_{i-1}. MDT reflects the time for the drug to dissolve and is the first statistical moment for the cumulative dissolution process that provides an accurate drug release rate. It is accurate expression for drug release rate. A higher MDT value indicates greater drug retarding ability.[9-12]

RESULTS AND DISCUSSION:

Phase solubility

Phase solubility analysis is among the preliminary requirements for optimization of the development into inclusion complexes of the drugs which can be used for evaluation of the affinity between CD's and drug molecule in water. Albeit CD's are known to generate aggregates (self-associates) in aqueous solvents,[13-16] the method is widely used for the determination of the molar ratios in drugs-CD complexes with CD's. The phase solubility curve of IRB showed a linear increase in solubility of IRB with an increase in concentrations of CD's in water (Fig 2.). Solubility of IRB is increased by 9.8-fold and 11.3-fold at 37 ºC at 15 mM concentrations of *b*-CD and HP-ß-CD, respectively. The Gibbs free energy of transfer ($\triangle G_{tr}^0$) of IRB from pure water to aqueous solutions of CD's was calculated using the values from phase solubility curve (Fig. 2) and applying the equation mentioned below.

$$\Delta G_{tr}^0 = -2.303\ RT \log (So / Ss)$$

Where, So/Ss = the ratio of molar solubility of IRB in aqueous solution of CD's to that of the pure water.[17] The obtained values of $?G_{tr}^0$ are shown in Table 2. In the present experiment $\triangle G_{tr}^0$ values were all negative for CD's at various concentrations, suggesting the spontaneous nature of IRB solubilization. These values further indicate greater degree of solubility improvement with HP-ß-CD as compared to ß-CD. The phase solubility plot showed an A_L type solubility curve for both the CD's, which indicated formation of inclusion complex of IRB in 1:1 stoichimetric ratio with ß-CD and HPß-CD. The stability constants (Ks) for the complexes at 37 ^{0}C, assuming a 1:1 stoichiometry, calculated from the slope of the phase solubility curve were 498 M^{-1} for ß-CD: IRB and 640 M^{-1} for HP-ß-CD:IRB, which indicated stable complex formation. Since Ks of HP-ß-CD:IRB and ß-CD: IRB in the range of 200–5000 M^{-1} there is an increase in the dissolution profile which would certainly increase bioavailability of IRB.

Drug content

The drug content of the PMB, PMH, KNB, COB, KNH and COH were found to be 97.73% (±2.83), 93.16% (±5.37), 90.44% (±13.18), 90.37% (±9.11), 93.34% (±2.91), and 93.01% (±3.43), respectively.

Characterization of complexes

Fourier transform Infrared (FT-IR) Spectroscopic analysis

The FT-IR spectra of PMB, KNB, COB, PMH, KNH and COH were compared with spectra of ß-CD, HPß-CD and IRB (Fig. 3). The spectrum of pure IRB depicts the characteristic peaks at 3441 cm^{-1} (N-H stretch), 3131 $cm^{-1}$and 3057 cm^{-1} (Aromatic C–H stretch), 2959, 2934, 2870, 2664, 2359 cm^{-1} (Aliphatic C-H stretch) 1732 cm^{-1} (C = O stretch), 1620 cm^{-1} and 1533 cm^{-1} (Aromatic C=C Bend and Stretch), 1441 and 1414 cm^{-1} (C–N amide stretch), 1358 & 1341cm^{-1} (C=O ketone) 746cm^{-1} (ring vibration due to 1,2-disubstituted benzene), respectively. The FT-IR spectra of ß-CD and HP-ß-CD are characterized by intense bands at 3300–3500 cm^{-1}due to O–H stretching vibrations. The vibration of the –CH and CH_2 groups appears in the 2800–3000 cm^{-1} region. The presence or absence of characteristic peaks associated with specific structural groups of the drug molecule was noted. The chemical interaction has been reflected by changes in the characteristic peaks of IRB, depending on the degree of interaction. The FT-IR spectra of PMB, KNB, COB, PMH, KNH and COH showed shift in peaks than those of CD's and IRB indicating chemical interaction between CD's and IRB during coevaporation, kneading, and physical mixing. The FT-IR spectras showed the absence of the characteristic peak of IRB at 3441.12 cm^{-1} (N-H stretch), 2958.90 cm^{-1} (aliphatic C-H stretch), 1357.93 cm–1(C=O ketone), 746.48 cm^{-1} (ring vibration due to1,2-disubstituted benzene), in complexes, indicating inclusion of IRB in CD's cavity in them. Hence it could be presumed the formation of inclusion of tetrazole ring and 1, 2- disubstituted benzene ring of IRB in the cyclodextrin complexes.

Powder X-ray diffraction (PXRD) analysis

Powder X-ray diffraction spectroscopy (PXRD) has been used to assess the degree of crystallinity of the given sample. When complexes of drug and CD's are formed, there was increase in amorphousness and consequently solubility of drug. The PXRD spectra's of all the samples are shown in Fig.4. Irbesartan spectra depicts major peak at 2θ values of 7.62, 10.33, 14.23, 14.63, 15.41, 18.66, 19.73, 20.7, 21.86, 22.73, 23.61, 24.26, 25.03, 27.61 & 29.66. while ß-cyclodextrin spectra showed major peaks at 2θ values of 5.07, 8.87, 9.65, 11.87, 13.61, 17.16, 19.83, 21.06, 23.48, 26.76 & 29.93. Due to amorphous nature of HPß-CD, no major peaks were detected in its spectra. Degree of crystallinity was decreased to maximum extent in case of complexes prepared using HPß-CD than ß-CD. Hence, from present structural data of complexes, it can be confirmed that inclusion of IRB in CD's cavity has been occurred.

Differential scanning calorimetry (DSC) analysis

Differential scanning calorimetry analysis has largely been used to detect all processes in which energy is required or produced. The thermograms of all samples are presented in Fig. 5. The IRB showed a melting peak at 184^{0}C. In the thermogram of the ß-CD and HPß-CD peak between 75 ^{0}C –125 ^{0}C was due to loss of water from CD's molecules. In the thermogram of all samples, peaks due to ß-CD and HPß-CD were observed at the same position i.e. between 75 ^{0}C–125 ^{0}C. Peak of IRB at 184 ^{0}C was present at the same position i.e. near to 184 ^{0}C in PMB, COB, PMH, and COH. In case of KNH and KNB, IRB peak is almost disappeared this may be attributed to trapping of IRB in the CD's cavity. This further confirms that kneading method is the best method for the preparation of inclusion complexes.

Dissolution studies

The dissolution studies was carried out with IRB and it's complexes and physical mixture using dissolution medium 0.1 N HCl. DP_{30} min (percent drug dissolved within 30 min), time to dissolve 50% drug (t_{50}%) and mean dissolution time (MDT) are reported in Table 3. The data revealed the onset of dissolution of pure IRB was very low in (29.93% within 30 min). COH, KNH, COB, and KNB significantly enhanced dissolution rates within 30 min as compared to pure IRB, PMB and PMH; see Fig. 6. It is evident that the dissolution rate of pure IRB is very low (49.46 % in 4 hr.) Inclusion complexes KNB, COB, KNH and COH significantly enhanced dissolution rate of IRB (75–81% within 4 h). The likely factors responsible for the improvement in

Table 1: Abbreviations used to designate different samples

Type of CD's	Method of preparation	Abbreviation used
ß–CD	Physical mixture	PMB
ß-CD	Coevaporation	COB
ß-CD	Kneading	KNB
HP ß–CD	Physical mixture	PMH
HP ß–CD	Coevaporation	COH
HP ß–CD	Kneading	KNH

Table 2. Gibbs free energy of transfer ($\triangle G_{tr}^{0}$) for solubilization process of IRB in aqueous solutions of cyclodextrins at 37 ^{0}C

Concentration of Cyclodextrins (mM/L)	$\triangle G_{tr}^{0}$ (kJ/mol) at 37 ^{0}C	
	ß–CD	HP ß–CD
3	-4.0781506	-4.2937319
6	-5.9774815	-6.194767
9	-7.0000015	-7.3553272
12	-7.8665872	-8.1656743
15	-8.4332337	-8.9683525

Table 3. $DP_{30\ min}$, $t_{50\%}$ and MDT values for release of IRB from different samples in 0.1 N HCl

Sample	% IRB Release					
	$DP_{30\ min}$		$t_{50\%}$ (min)		MDT (min)	
	Complex	Tablet	Complex	Tablet	Complex	Tablet
Pure IRB	29.93	24.21	>240	>240	52.43	62.58
PMB	40.51	——	74.18	——	32.30	——
COB	55.87	43.11	14.36	59.74	30.70	45.81
KNB	**62.73**	**45.36**	**12.98**	**34.83**	**30.09**	**44.84**
PMH	46.54	——	68.09	——	31.89	——
COH	63.16	49.93	13.91	30.69	29.86	41.74
KNH	**69.96**	**50.77**	**12.62**	**29.56**	**28.05**	**38.90**

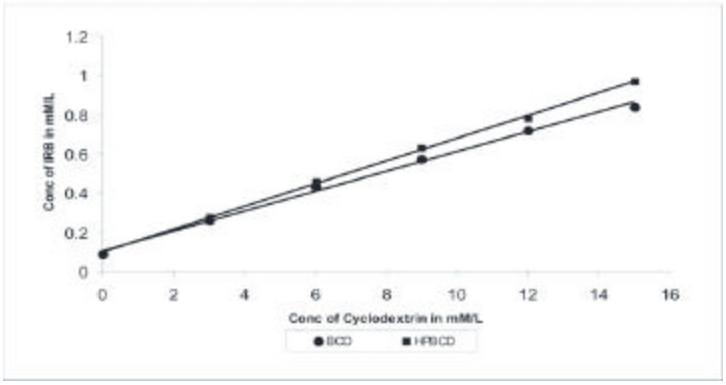
Table 4. f_2 values for comparison between release profiles of IRB from complex and PM's in 0.1 N HCl.

Sample	PMB	COB	KNB	PMH	COH	KNH
Pure IRB	42.64	26.25	**22.04**	41.39	22.89	**19.29**
PMB	—	39.45	32.22	90.98	33.43	27.97
COB	—	—	58.15	40.68	62.66	46.57
KNB	—	—	—	33.1	79.6	63.95
PMH	—	—	—	—	34.36	28.71
COH	—	—	—	—	—	58.48

Table 5. Physical properties of complexes and tablets

Physical Property	Pure IRB	COB	KNB	COH	KNH
% Compressibility	11.21	12.36	13.64	12.08	14.27
Angle of repose	22.41	24.37	25.39	26.18	27.14
Hardness (Kg/cm^2)	4.3	4.4	4.5	4.6	4.4
Friability (%)	1.8	1.6	1.4	1.5	1.6
Diameter (mm)	8	7.5	8	7.5	8
Thickness (mm)	4	5	5	4.5	5

Fig 2: Phase solubility curve of IRB in aqueous solution of ß-CD & HPß-CD at 37 ^{0}C



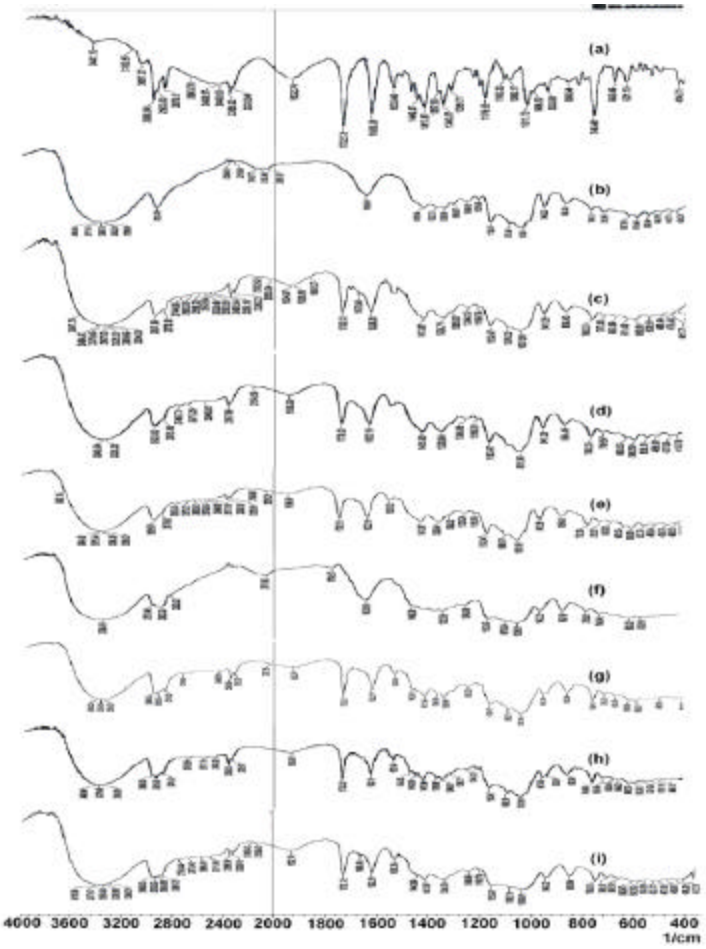


Fig 3: FT IR Spectra of Irbesartan, CD's and its complexes (a) IRB, (b) ß-CD, (c) PMB, (d) COB, (e)KNB, (f) HP ß–CD, (g) PMH, (h) COH, (i) KNH

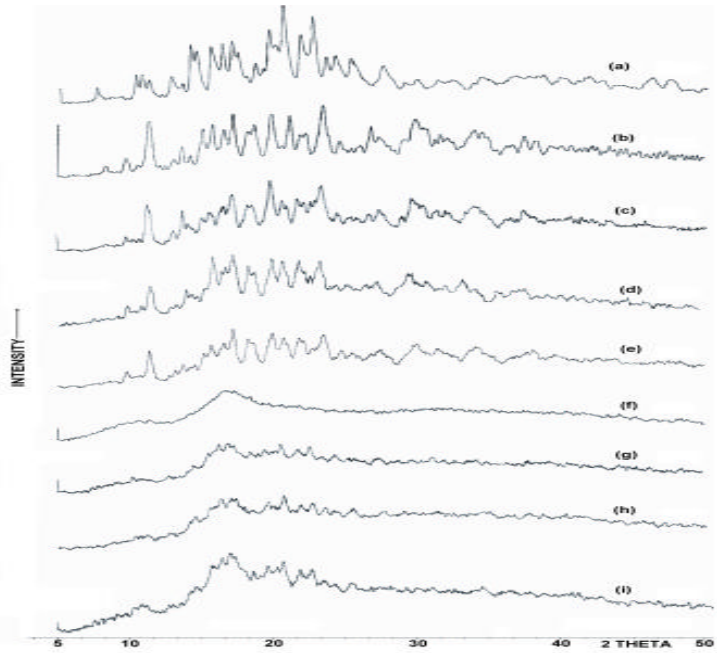


Fig 4: PXRD Spectra of Irbesartan, CD's and its complexes (a) IRB, (b) ß-CD, (c) PMB, (d) COB, (e)KNB, (f) HP ß–CD, (g) PMH, (h) COH, (i) KNH

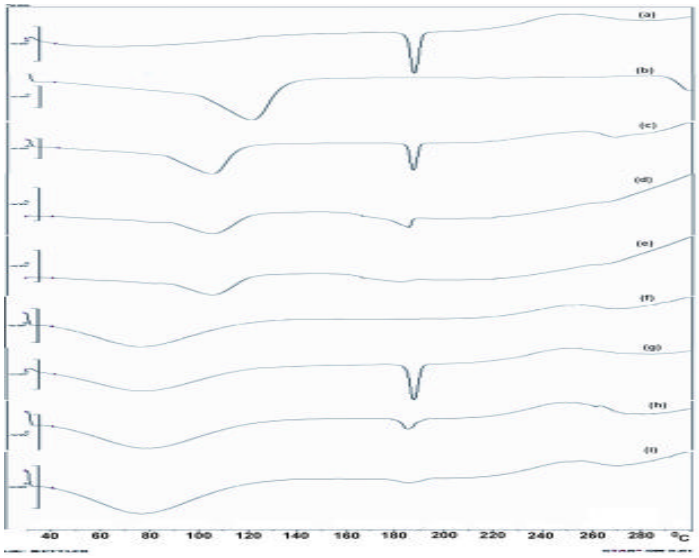


Fig 5: DSC thermograms of Irbesartan, CD's and its complexes (a) IRB, (b) ß –CD, (c) PMB, (d) COB, (e)KNB, (f) HP ß –CD, (g) PMH, (h) COH, (i) KNH

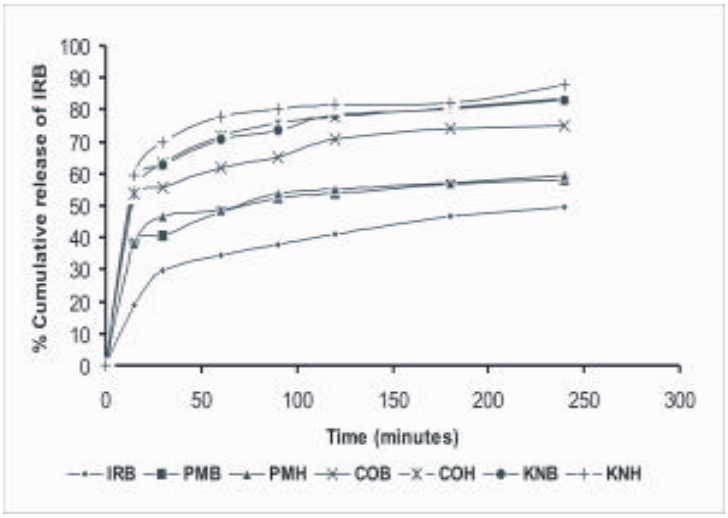


Fig 6: In vitro dissolution profiles of IRB, its physical mixture & complexes in 0.1 N HCl

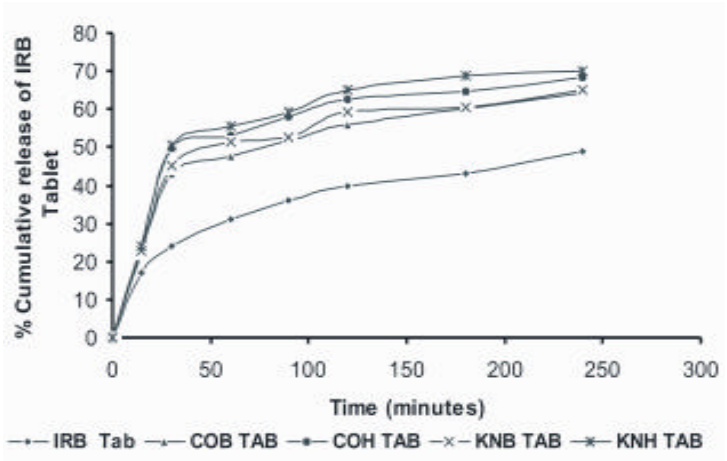


Fig 7: Release profiles IRB from conventional tablets containing only IRB and tablets containing KNB, COB, KNH and COH in 0.1 N HCl

dissolution rates of complexes & PM's are; reduction of crystal size, solubilization effect of carrier, improved wettability etc. MDT of IRB was 52.43 min in dissolution medium.[18] The MDT values of IRB decreased to greater extent after preparing complex of IRB with CD's i.e. 30.70 min, 30.09 min 29.86 min & 28.05 min for COB, KNB, COH and KNH respectively. Complexes prepared by coevaporation and kneading method exhibited enhanced dissolution profile and lower MDT values, were taken as an important paradigm for the formulation studies. Calculated f2 values (Table 4) indicate that the release profile of COH and KNH is significantly different from pure IRB (f2 values 22.89 and 19.29) which further explains that complexes with HP-ß-CD gives better dissolution results than ß-CD.

Formulation studies

The complexes prepared by kneading and coevaporation method (KNB, COB, KNH and COH) were studied for physical properties to judge its tableting suitability. In general, compressibility index values up to 15% and angle of repose between 25^0 and 30^0 often found to result in good to excellent flow properties. Percent compressibility, angle of repose for complexes and physical properties of tablets made using these complexes are shown in Table 5. These values indicated good compressibility and flow properties, making these samples suitable for tableting. The tablets prepared using complexes showed faster and reproducible release as compared to the tablets containing pure IRB and no CD's. Tablets prepared using COH & KNH showed 68.28 and 70.17% release in 4 h with t_{50}% of 30.69 min and 29.56 min, respectively (Fig. 7) indicating effectiveness of HP-ß-CD over ß-CD. Tablets prepared using COB and KNB also exhibited better dissolution profiles as compared to tablets prepared using IRB alone. These results clearly point out the advantage of improved aqueous solubility of IRB in its complex form, which can be formulated as tablets with better dissolution pattern. Release profiles of IRB from tablets containing IRB alone are significantly different from tablets containing COH and KNH as the f2 values were 34.16 & 32.09. MDT of IRB from tablets containing COH and KNH were (41.74 & 38.90 min) significantly lower than that of tablets containing only IRB (Table 3).

CONCLUSION:

Solubility studies showed a significant, linear increase in the aqueous solubility of Irbesartan with increasing concentrations of ß-CD and HPß-CD. The highest improvement in solubility and *in vitro* drug release were observed in inclusion complex prepared with HPß-CD by kneading method. Improvement in solubility and drug release of Irbesartan were more with HPß-CD as compared to ß-CD. The findings suggest that prepared complex with HP-ß-CD showed greater dissolution profile of IRB. Further similar improved dissolution with tablets formulated with HP-ß-CD inclusion complex of IRB.

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